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Title:

Compounds

Technical field of the invention:

The present invention relates to novel compounds for use as pharmaceuticals. More particularly the invention relates to novel compounds for the use as diagnostic agents and in a preferred aspect for the use in X-ray investigations.

Background of the invention:

It is known from the state of the art that various heavy chemical elements potentially have properties useful as pharmaceuticals. More particularly they can be used as diagnostic agents e.g. in MRI, electrical impedance imaging, magnetomeric imaging modalities and specific heavy elements have potential in the use as X-ray contrast agents due to their high X-ray contrast attenuation.

For X-ray imaging potentially useful elements as contrast agents are listed in table 1 below. This table presents data for a series of measurements of X-ray attenuation for a number of elements. The values are relative values where the value of iodine is set to one, at 120 keV electron energy. The last column provides the relative X-ray attenuations, where the X-ray attenuations of equal-sized spheres of the different elements are compared. These X-ray attenuations are based on measurements made on solutions of equal weight concentrations of the different elements and calculated based on the elements' density where the value for one iodine atom is set to 1. The sphere is used as an approximation of the disclosed compact cores. Clusters in the nanometer range tend to adopt polyhedral shapes, as described by R.L. Johnson, Atomic and molecular clusters, pages 102-107.

Table 1.

Element	Relative molar extinction	Density of element g/m^3	No. atoms in 3 nm sphere	Relative attenuation for equal sized spheres
I	1	4.93×10^6	330	1
Ba	1.4	3.59×10^6	222	0.94
Gd	1.9	7.90×10^6	427	2.45
Er	2.2	9.07×10^6	461	3.07
W	1.7	19.3×10^6	893	4.59

Pt	1.8	21.5×10^6	938	5.10
Bi	2.1	9.78×10^6	398	2.52
U	2.2	19.1×10^6	683	4.54
Au	1.8	19.3×10^6	833	4.54

As will be evident from table 1 the most preferred elements for use as X-ray contrast agents based on their relative attenuation are Pt, W, U, and Au.

One important issue is the cost of the elements, which eliminate platinum, gold, gadolinium, erbium, iridium and the rest of the rare earth metals as viable candidates. These elements are too expensive for use in a commercially available X-ray contrast agent.

Uranium is not considered to be a viable candidate because of the issue of possible contamination of depleted uranium by ^{235}U and the general negative properties of uranium; hence uranium is not suitable for the use as an X-ray contrast agent. In addition the metallic element chosen should not be radioactive due to possible toxic side effects caused by the hazards of radiation.

Yet another factor is the toxicity of elemental mercury, thallium and lead, which eliminates these for use in contrast agents. This leaves tungsten and bismuth as candidates and the much higher density of tungsten makes this the better candidate.

Nanoparticles of metallic tungsten are hence viable candidates as contrast agents for X-ray imaging, given the high attenuation, low cost and low toxicity.

However, nanoparticulate metallic tungsten is very reactive and nano-crystalline tungsten powder ignites spontaneous in air. J. Mater. Res., Vol. 15, No. 7, Jul 2000, pages 1564-1569 describes the formation of tungsten nanoparticles from $W(CO)_6$. It is demonstrated that these nanoparticles must be kept under an inert atmosphere of nitrogen gas preventing the particles from a spontaneous reaction with air oxygen.

Description of related prior art:

Non-ionic, Iodinated X-ray contrast agents dominate the diagnostic imaging field, except for gastrointestinal investigations where $BaSO_4$ suspensions are used.

WO 03/075961 describes in one aspect the use of coated gold particles as X-ray contrast agents. In a preferred aspect use of thioglucose as a coating-layer is described and the particles are excreted from the body by the kidneys or the liver depending on the particle size. In another aspect targeting moieties are present in the coating for imaging of specific organs.

Langmuir, Vol. 15, No 1. 1999, 15, pages 66-76 describes water-soluble, mono-layer protected gold clusters, a process for making such compounds and their characterisation.

EP-B1-521,977, EP-B1-577,675, EP-B1-831,934 and EP-B1-876161 describe the use of multinuclear complexes for X-ray investigation which comprise mainly the use of tungsten sulphides, sulphates, oxides and iodides for X-ray investigations.

There is, however, still a need for new diagnostic products specifically for the use as X-ray contrast agents with improved properties over existing contrast agents. This invention relates to contrast agents, which have improved properties over the existing products regarding several important characteristics.

Summary of the Invention:

It has now surprisingly been found that pharmaceuticals based on nanoparticulate tungsten particles can be provided that are useful as diagnostic agents, in particular as X-ray contrast agents. The novel particles comprise a core of the metallic element tungsten optionally mixed with other metallic elements wherein said core is coated with a hydrophilic layer. The coating passivates the reactive surface of the tungsten particles to make them non-reactive in air, solvents and when administrated to subjects in-vivo and during the conversion and excretion.

Detailed description of the invention:

The particle core according to the invention comprises the metallic element tungsten or the metallic element tungsten mixed with other metallic elements, preferably with a tungsten content of 20-100 weight % or, more preferably with a tungsten content of 50-100 weight % or, even more preferably with a tungsten content of 85-100 weight % or, especially preferably with a tungsten content of 95-100 weight %.

In a preferred aspect of the invention the tungsten metallic element core comprises between 15 and 5000 tungsten atoms and in a more preferred aspect the tungsten metallic element core comprises between 100 and 1500 tungsten atoms.

Table 2 below indicates the size of particles packed in body centred cubic crystals. This table indicates the number of atoms in each particle and their size in nanometre (nm).

Table 2.

No shells	No atom	Core diameter (nm)	Core + coat diameter (nm)	Coating thickness (nm)
1	15	0,632	1,832	0,6
2	65	1,264	2,464	
3	175	1,896	3,096	
4	359	2,528	3,728	
5	671	3,16	4,36	
6	1105	3,792	4,992	
7	1695	4,424	5,624	
8	2465	5,056	6,256	
9	3439	5,688	6,888	
10	4641	6,32	7,52	

The particle according to the invention has a diameter which is in the range of nanometres (nm). In a preferred aspect the diameter of the particle is between 1.5 and 10 nm. In a more preferred aspect the diameter is between 2 and 5 nm. This size is an important parameter because it decides how the particles are eliminated from the body. The kidney particle threshold is about 4 to 5 nm. It is preferred that the particles are excreted through the kidneys and not through the bile. Particles of 4 to 5 nm size would have the advantage of slow extravasation so it would, at least for a time span sufficient for X-ray investigations, function as a blood-pool contrast agent with the increased contrast of vessels over tissue that follows.

In another aspect of the invention other heavy elements could be introduced to the tungsten metallic core. This could be done to improve stability, monodispersity, the synthesis and rate of formation of the core. In this aspect of the invention it is preferred to include a concentration of between 5-15 weight % rhenium, iridium, niobium, tantalum or molybdenum either as a single element or as mixtures of these elements. It is well known that these elements are known to be miscible with tungsten and may be useful in this application. In a more preferred aspect it is preferred to have a concentration of between 5-15 weight % rhenium or iridium either as a single element or as mixtures of these elements. Small amounts of the elements

rhenium and iridium improves the low-temperature plasticity of tungsten, which may be advantageous for the properties of the nano-particles, see Lassner, Erik; Schubert, Wolf-Dieter; "Tungsten properties, chemistry, technology of the element, and chemical compounds" Kluwer Academic, NY, 1999 page 28 and page 256.

By the term metallic element is meant a material that shows typical metallic properties in the bulk phase. Some of these properties are high electric conductivity, high thermal conductivity, ductility, and reflectivity. They are all effects of the extensive delocalisation of the electrons in the metal lattice, which in turn makes the band-gap small enough to be populated by thermal excitation. The metallic properties start to appear in the range of sizes of particles according to the invention, when the numbers of atoms are in the range from tens to thousands of atoms.

The core is coated with a hydrophilic layer. The coating should be a layer of non-metallic atoms comprising at least a fraction of molecules that are hydrophilic and preferably each molecule should have at least one hydrophilic group. The coating should at the same time cover the tungsten surface densely enough to passivate it. It is necessary to passivate the tungsten core since tungsten particles without coating are highly reactive. This passivation takes place on the surface of the tungsten core where there is an electron transfer between the metal coordination group and the surface of the tungsten core. In a preferred aspect the coating is a mono-layer coating meaning that the thickness of the coating is only one single molecule. Such coatings are preferred over polymeric coatings since the layer can be made thinner and with well defined properties. It is important with a thin layer coating since the efficacy depends on the number of tungsten atoms that constitute the particle and the total diameter of the particle is limited by the kidney excretion threshold. The oriented mono molecular layer also provides improved control over solubility and toxicology since there will be a well defined outer end of the molecule where the solubilizing groups can be placed and an end facing and binding to the metal.

In a preferred aspect of the invention the mono-layer coating is built according to the general formula A_n-L_o-M_p, where A is one or more tungsten coordinating groups preferably selected from Table 3, L is one or more linking groups preferably selected from Table 4, and M is one or more hydrophilic groups preferably selected from Table 5. The linking group preferably comprises any number of fragments from Table 4 arranged linearly, branched or in one or more rings. The branching may be towards the A group side to create multidentate coatings or it may branch towards the M

group to create a higher degree of hydrophilicity. Branching in both directions is also an option. Linking fragments from Table 4 may be combined to phenyl rings or aromatic or non-aromatic heterocyclic groups. n is any positive integer and preferably 1 to 10 or more preferably 1 to 4. o is zero or any positive integer and preferably 1 to 10 or more preferably 1 to 2. p is any positive integer and preferably 1 to 10 or more preferably 1 to 4. The dotted line indicates for A a bond to the tungsten element, a bond to an H-atom, a bond to the L-group, a bond to another A-group or a bond to the M group when o is zero. The dotted line indicates for L a bond to the A group, a bond to an H-atom, a bond to another L-group or a bond to the M-group. The dotted line indicates for M a bond to the L group, a bond to an H-atom, a bond to another M-group or a bond to the A-group when o is zero.

Table 3, Metal coordinating groups A:

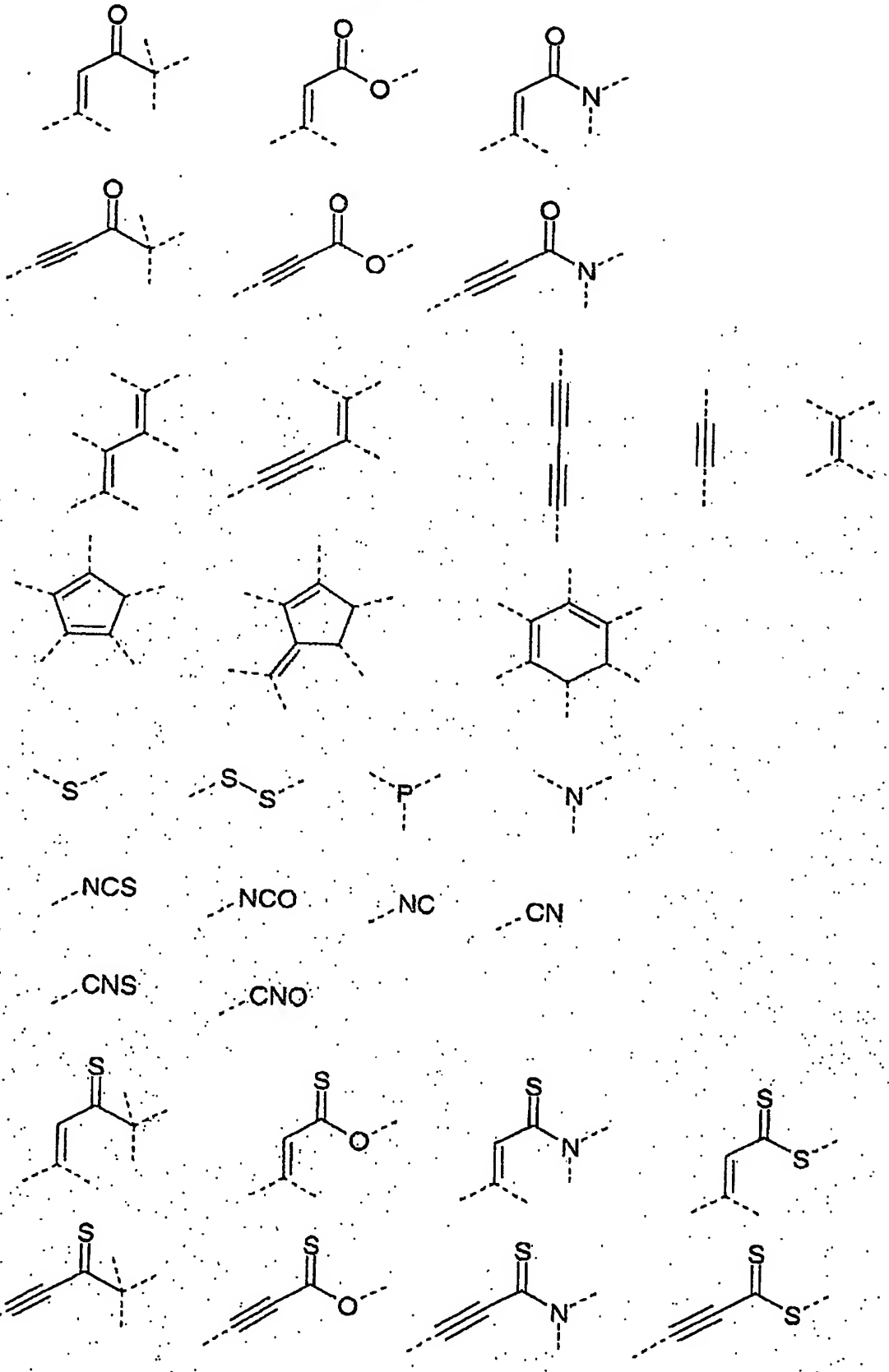


Table 4, Linking groups L:

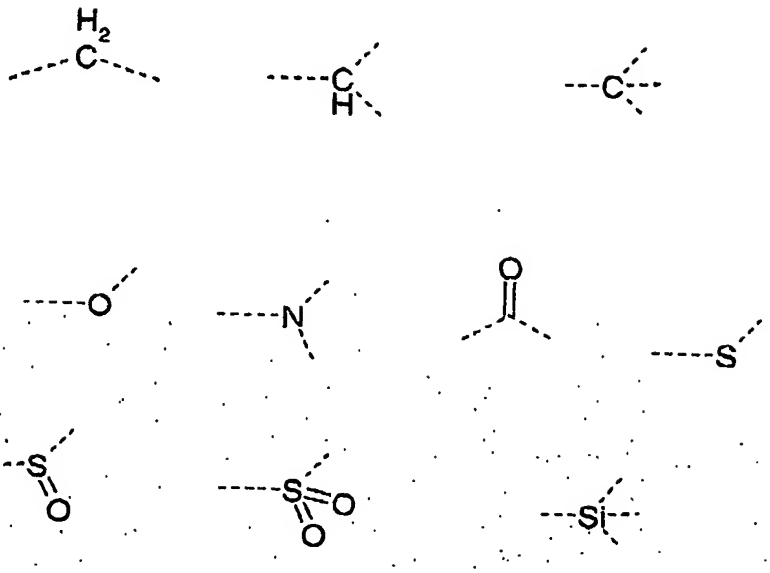
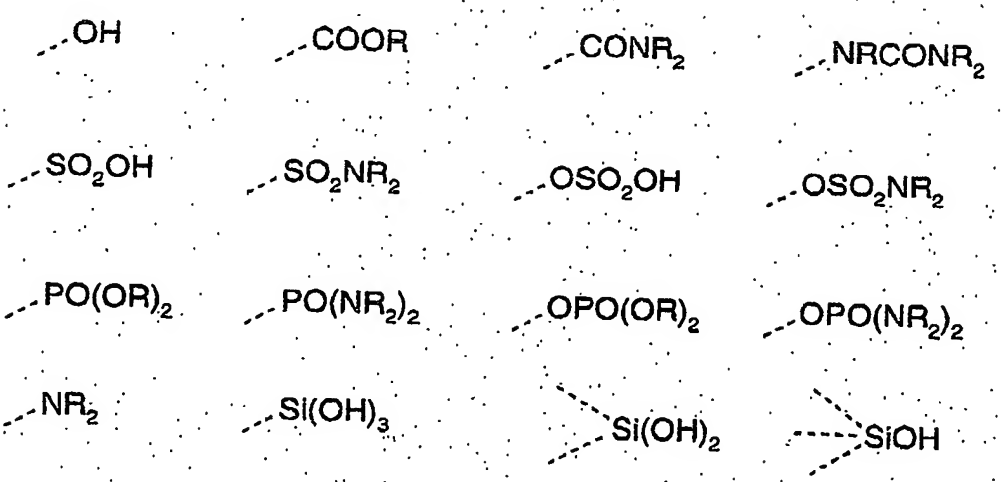


Table 5, Hydrophilic groups M:



The R - groups are independently any group(s) selected from H and a C_1-C_6 alkyl group optionally substituted by one or more –OH groups and where one or more of the C-atoms of the C_1-C_6 alkyl group may be replaced by an ether group.

In the comparison of coated tungsten and coated gold particles any ligands, e.g. any sulphur ligands, in the coating of the gold particles are exchangeable. This means that the binding between the surface of the gold particles and the coating is not strong and the coated gold particles will hence tend to have a long half-life in the

body because of exchange of the ligands in the coating with groups in the tissue e.g. protein sulfhydryl groups. This means that uncoated gold particles will remain in the blood stream, see e.g. Hostetler, M.J.; Templeton, A.C.; Murray, R.W; "Dynamics of Place-Exchange Reactions on Monolayer-Protected Gold Cluster Molecules" Langmuir, 1999, 15, 3782-3789. The long half-life in the body is not desirable because this could lead to higher toxicity and the long half-life is not at all an advantage in X-ray investigations. However for the tungsten particles of this invention the surface of the tungsten core will be more irreversibly bound to the ligands of the coating layer and hence they will have low affinity for the tissue. Accordingly the coated tungsten particles will be excreted faster via the kidneys.

A comparison of performance of the particles according to the invention to a monomeric iodine contrast agent has been calculated.

The viscosity of particles of the invention:
The volume fraction of the contrast agent Iopamidol in an aqueous solution at 350 mg Iodine/ml is 0.26 and the viscosity is 7.6 mPas at 37ºC. Assuming that we can use the same volume fraction ϕ=0.26 for the particles according to the invention, where the viscosity of the solvent $\eta_0 = 0.653\ 10^{-3}$ Pas for water at 37ºC, the visoosity η of such solution at 37ºC would then be:

$$\eta = \eta_0 \exp[\tfrac{5}{2}\phi/(1-0.75\phi)] \approx 1.46\ \text{mPas (I)}$$

(see "The viscosity of a concentrated suspension of spherical particles" Mooney, M.J. Colloid. Sci. vol. 6, page 162, (1951)). This viscosity is very low for such a high concentration of particles and relies on the assumption that it is a solution of rigid spheres. This viscosity is also low compared to the viscosity of iodinated X-ray contrast agents.

The X-ray attenuation aspect of the invention:
In table 2 it is indicated that particles with a diameter of less than 5 nm can contain more than 1000 core atoms. This means that it is possible to make a solution with a high concentration of tungsten atoms. Further this indicates that an improvement in X-ray attenuation over commercially available X-ray contrast agents can be achieved.

The particles of the invention are preferably administrated as a pharmaceutical formulation in a form suitable for administration to a mammal, such as a human. The administration is suitable carried out by injection, infusion or oral use of the formulation such as an aqueous solution. The formulation may contain one or more pharmaceutical acceptable additive and/or excipients.

The cores of the particles according to the invention can be prepared by a reduction of tungsten ions to form metallic tungsten and formation of nano-sized particles. This formation of particles demands strict control of the growth of the particles during the reduction. This control can be accomplished by the use of a compound that reacts with, and attaches itself to the metal surface of the cores. The metal / surface-binding compound ratio determines the size of the particles.

The particle can also be prepared e.g. according to Langmur, Vol. 15, No. 1, 1999, page 66-76. This article describes a process for the preparation of mono-layer protected gold particles and this process can be used by choosing an appropriate tungsten metal-source known to the skilled man. As is well known in the art, it is possible to influence the size of particles by adding surfactants to the reaction mixture.

Alternatively the preparation can start from a source of tungsten (0) such as $W(CO)_6$, which in one or more steps is converted to coated metal particles by the controlled displacement of the carbonyl ligands.

The invention will hereinafter be illustrated with the non-limiting examples:

Example 1: Preparation of tungsten nano-particles by reduction in an organic solvent

The reaction is performed under inert gas. A tungsten compound (e.g. WCl_6) and a coating where reactive sites are protected by protection groups are dissolved in an aprotic, water immiscible organic solvent and a soluble reduction agent is added. After the reaction is complete, water and organic solvent are added and the phases are separated. The organic layer is washed with water and evaporated to a small volume. A large excess of ethanol/water is added and the solids are allowed to precipitate. The solids are filtered off and the dissolution, precipitation procedure is repeated once more. The particles are dried in vacuum.

The protecting groups are removed by a suitable procedure. If necessary the solution is desalinated by dialysis, size exclusion chromatography, or some other suitable technique. The final product is typically obtained by freeze drying.

Example 2: Preparation of tungsten nano-particles by reduction in water

A water-soluble tungsten compound e.g. sodium tungstate and a coating molecule are dissolved in deoxygenated water under an inert atmosphere. The pH is adjusted to a desired value. This solution is then added to a vigorously stirred solution of reducing agent in degassed water. After complete reduction, the solution is reduced in volume, desalinated by dialysis and then freeze dried to give the final product.

Example 3: Preparation of tungsten nano-particles by reduction in inverse micelles

An aqueous solution of a water soluble tungsten compound, e. g. sodium tungstate adjusted to a desired pH is introduced as the aqueous phase into an inverse micelle in an organic solvent by the addition of a large fraction of surfactant. A similar inverse micelle formulation of an aqueous reduction agent is also made. The tungsten containing liquid is added to the reduction agent. Coating molecules are added. After equilibration, water is added to break the emulsion. The aqueous phase is collected and the organic phase is washed with two more portions of water. The collected aqueous phases are reduced in volume and desalinated by dialysis. The aqueous solution is then freeze dried to give the final product.

Example 4: Preparation of tungsten nanoparticles by decomposition of a tungsten (0) complex

A thermally labile W(0) complex, e.g. W(CO)6 is decomposed in an inert, high boiling solvent, e.g. cyclooctane, in the presence of coating molecules where reactive sites are protected by protection groups, e.g. hexylacrylate. After completed reaction, a polar solvent such as ethanol is added; the black powder is filtered of and washed.

The protecting groups are removed by e.g. hydrolysis or other suitable procedure. The solution is reduced in volume and desalinated. The aqueous solution is then freeze dried to give the final product.

Example 5: Synthesis of N,N-bis(2-hydroxyethyl)acrylate-coated tungsten nano-particles

The reaction is carried out under air free conditions. Tungsten hexacarbonyl and N,N-bis(2-dimethyl-tert-butylsilyloxyethyl)acrylate are dissolved in cyclooctane and heated to reflux for 12 hours. Most of the solvent is removed in vacuum and the black residue is washed three times with methanol.

The protecting groups are removed by hydrolysis in 10% aqueous formic acid. The liquids are evaporated, the residue dissolved in water and taken to dryness again. The product is formed as a black powder, wherein the coating layer comprises the molecule $H_2C=C-CO-N\ (CH_2-CH_2OH)_2$.

Claims

1. A particle comprising a core of the metallic element tungsten optionally mixed with other metallic elements wherein said core is coated with a hydrophilic layer.

2. A particle as claimed in claim 1 wherein said core comprises 20-100 weight % tungsten.

3. A particle as claimed in claims 1 or 2 having a diameter between 1.5 and 10 nm.

4. A particle as claimed in claim 3 having a diameter between 2 and 5 nm.

5. A particle as claimed in any of the claims 1-4 wherein said core comprises between 15 and 5000 tungsten atoms.

6. A particle metallic element core as claimed in claim 5 wherein said core comprises between 100 and 1500 tungsten atoms.

7. A particle as claimed in any of the claims 1-6 wherein said hydrophilic layer comprises at least a fraction of molecules that are hydrophilic.

8. A particle as claimed in any of the claims 1-7 wherein said hydrophilic layer comprises molecules that each has at least one hydrophilic group.

9. A particle as claimed in any of the claims 1-8 wherein said core is coated with a mono-layer coating.

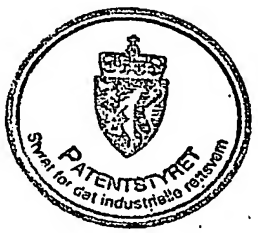
10. A particle as claimed in claim 9 wherein said mono-layer coating is passivating the core.

11. A particle as claimed in claims 9-10 wherein the mono-layer coating comprises compounds of formula A_n-L_o-M_p, where A is one or more tungsten coordinating groups, L is one or more linking groups and M is one or more hydrophilic groups, n and p are positive integers and o is zero or a positive integer.

12. A diagnostic agent comprising a particle as claimed in claims 1-11.

13. An X-ray contrast agent comprising a particle as claimed in claims 1-11.

14. A pharmaceutical acceptable formulation of particles as claimed in clam 1-11 for the use as a contrast agent.



Abstract:

The present invention relates to novel compounds for use as pharmaceuticals. More particularly the invention relates to novel compounds for the use as diagnostic agents and in a preferred aspect for the use in X-ray investigations. The novel compounds are particles comprising a core of the metallic element tungsten optionally mixed with other metallic elements wherein said core is coated with a hydrophilic layer.

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